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Adenocarcinoma of the Kidney: Nephron-Sparing Surgical Approach vs. Radical Nephrectomy

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Background and Objectives: Radical nephrectomy has been the traditional surgical treatment for renal cell carcinoma in patients with a normally functioning contralateral kidney. The necessity for a less aggressive surgical approach has emerged in cases in which there is a need to preserve renal function.

Methods: We retrospectively evaluated the records of 41 patients with localized, symptomless small renal masses (<5 cm) treated with nephron-sparing surgery (group A) and 48 patients matched for age, tumor location, size, and stage who were treated with radical nephrectomy (group B).

Results: The 5-year cancer-specific survival rates were 97.5% and 98.4% for the treated patients of groups A an B, respectively. No statistical association was found between cancer-specific survival and surgical approach, tumor stage, tumor location, or recurrence. The size of the primary tumor did not seem to influence the cause-specific survival. Local recurrence was observed in 3 patients (7.3%) who underwent partial nephrectomy. In our series, the overall incidence of multifocality was 10.4%.

Conclusions: We propose segmental renal resection for unifocal small adenocarcinoma of the kidney in preference to radical surgery as it is corroborated by the presented data.

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KEY WORDS: **nephron-sparing nephrectomy; radical nephrectomy; renal cancer**

INTRODUCTION

Radical nephrectomy has been the time-honored surgical treatment for renal cell carcinoma in patients with a normally functioning contralateral kidney [1,2]. The necessity for a less aggressive surgical excision has emerged in cases in which there is a need to preserve renal function [3].

The current indications for partial nephrectomy include situations in which radical nephrectomy would definitely compromise the overall renal function. Such conditions concern patients with bilateral renal cell carcinoma or renal cell carcinoma involving a solitary functioning kidney where nephrectomy (bilateral or unilateral) would necessitate chronic hemodialysis. Partial nephrectomy is also considered an appropriate choice in patients with a unilateral renal tumor and a functioning contralateral kidney affected by a benign condition that may threaten its future function. Such conditions are nephrolithiasis, ureteral reflux, chronic pyelonephritis, and renal artery stenosis or systemic diseases such as diabetes, nephrosclerosis, or collagen disease [4–8].

Contrary to former beliefs for von Hippel-Lindau disease, Novick [9,10] reported that the results of nephron-

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sparing surgery in those patients are less satisfactory, followed by high recurrence rates due possibly to multicentricity of the lesions associated with this disease. The same author proposed that bilateral nephrectomy is indicated in the latter patients, who must undergo either hemodialysis or renal transplantation.

With the frequent use of ultrasonography and computed tomography (CT) for screening of intra-abdominal and retroperitoneal disease, incidental detection of asymptomatic renal tumors has increased. These asymptomatic renal masses are usually smaller and lower in stage than symptomatic ones [11].

Several investigators have reported on their experience with nephron-sparing surgery for selected patients with unilateral small renal masses and a normal contralateral kidney [12,13]. However, the use of partial nephrectomy has been and remains controversial. During recent years, we have practiced nephron-sparing procedures more frequently, with apparent good results.

To assess the outcome of our technique, we used this retrospective study to evaluate the pathological findings, local recurrence rate, survival, and complications in 41 patients who had nephron-sparing surgery. This group of patients was then statistically evaluated by comparison with another group of 48 patients, who were matched for age and for tumor location, size, and stage and were treated with radical nephrectomy during the same time period as the first group.

MATERIALS AND METHODS

Our study consisted of a retrospective analysis of 41 patients (group A) ranging in age from 44 to 71 years (mean, 64) with localized, symptomless renal masses who underwent nephron-sparing surgery at the Department of Urology, University of Patras, or at the Department of Urology, Metaxa Cancer Institute-Piraeus, from 1986 to 1996. Those patients were matched according to age and to tumor location, size, and stage with 48 patients (group B), 42–75 years old (mean, 66), who underwent radical nephrectomy during the same period.

In the two departments, the indications for nephron-sparing operation were the same: a solitary renal tumor <5 cm, absence of von Hippel-Lindau disease, lack of renal venous or vena caval involvement, existence of pseudocapsule on CT scan or magnetic resonance imaging (MRI) preoperative studies, absence of erratic growth of the mass into adjacent renal parenchyma, and lack of distant metastases.

The preoperative evaluation included, in all cases, chest radiograph, liver and renal function tests, and CT scan of the abdomen and pelvis with 1-cm section intervals. Further evaluation with transabdominal renal sonography, excretory urography, MRI, and renal angiography was performed selectively as indicated. Tumor staging in both groups followed the criteria set by the TNM system [14].

Surgical Technique

An extraperitoneal flank approach was preferred in all cases. Gerota's fascia was opened, and the kidney was completely mobilized except near the renal mass, where the perinephric fat was left attached to the renal capsule. After identification of the renal vascular pedicle and a complete draping of the surrounding tissues, the overlying mass fat was completely excised from the renal capsule and sent for frozen biopsy. The entire kidney was thoroughly washed with distilled water, and using intraoperative renal ultrasonography (IRU) in contact with the renal capsule, we were able to accurately localize the renal mass, its borders, and the relation to the corresponding renal calyx or calyces. Hypothermia in the form of ice slush (Ringer's lactate solution) was also used, providing a decrease of the renal tissue metabolism and oxygen requirements during the ischemic phase.

In sequence, the renal vessels were clamped, and completely excised the cancerous lesion with negligible bleeding. The tumor outline was marked with colored stiches with the aid of the ultrasonic probe, securing their placement at 1 cm beyond the pseudocapsule margin. A fluid field sterile glove was used to enhance our image accuracy during IRU. The resection involved removal of at least 1 cm of normal renal tissue surrounding the tumor mass. An intraoperative frozen section was sent for histopathological analysis in all cases, to ascertain negative tumor margins and to rule out possible extension of the malignancy through the capsule. A calicoplasty was performed to accurately close the opened calyx or calyces; after the renal pedicle was unclamped, any additional arterial spurters were ligated using 3-0 chromic cat-gut stitches. The ureter was temporarily occluded with a vascular tape and cannulated, and methylene blue solution was injected to ascertain the integrity of the collecting system. In case of leakage of the solution, further closure followed as needed.

At the end of the procedure, the secondarily created fossa due to the mass removal was inspected using an operating microscope to verify absence of suspicious residual tumorous tissue. Further ultrasonic search for satellite lumps was performed using a modification of our technique by applying the probe directly into the sides of the newly created fossa. This modification was applied to the last six patients in this series. For mid-section lesions of the kidney, the remaining upper and lower moieties were approximated by suturing with a round liver needle and tying over bolsters of either gortex material or fat mobilized from a region distant to the kidney.

The patients were evaluated 2, 6, and 12 months postoperatively and thereafter twice a year. The mean follow-up period was 4.9 years (range, 12–102 months). Post-

operative evaluation consisted of physical examination, blood and urine sample testing, chest radiographs, and CT scanning. CT was performed every 6 months for the first 2 years and thereafter once a year.

Statistical Methodology

In our methodology, we evaluated such parameters as surgical approach; tumor stage, location, and size; recurrence; multifocality; and presence of metastatic disease and their possible correlation to the observed cancer-specific survival.

For survival studies, the product-limit (Kaplan-Meier) estimate of survival is calculated by dividing time into intervals such that each interval ends at the time of an observation, whether censored or uncensored. The probability of survival is calculated at the end of each interval, with censored observations assumed to have occurred just after uncensored ones. The product-limit survival function is a step function that changes value at each time point associated with an uncensored value.

In survival analysis, a log-rank test compares the equality of k survival functions by creating a sequence of $k \times 2$ contingency tables (k survival functions by event observed/event not observed at that time), one at each (uncensored) observed event time, and calculating a statistic based on the observed and expected values for these contingency tables. This is also known as the Mantel-Cox (Mantel-Haenszel) test.

RESULTS

The postoperative course was essentially the same for both groups of patients in regard to hospitalization period, blood transfusion, and complications. All complications were minor and dealt with successfully. No patient needed hemodialysis postoperatively. Group A patients had a gradual decrease of creatinine clearance, which reached its maximum at 4 years after surgery but remained within the normal range. In six patients, proteinuria was observed but was <100 mg/day. In group B patients, creatinine clearance remained at lower numerical levels, which when compared to the corresponding levels of group A did not reach a statistically significant difference ($P > 0.01$). Proteinuria was not observed in group A (Table I).

Of the 41 patients (group A) who underwent nephron-sparing surgery, 10 (24.4%) were classified as T1 lesions, 28 (68.3%) as T2, and 3 (7.3%) as T3a. Among the 48 patients (group B) who underwent radical nephrectomy, 9 (18.7%) were classified as T1 lesions, 35 (72.9%) as T2, and 4 (8.3%) as T3a (Table II).

The 5-year cancer-specific survival rates were 97.5% and 98.4% for the treated patients of groups A and B, respectively (Figs. 1, 2). Statistically, the null hypothesis was that the survival curves are identical in the overall population (of both groups). The *P* value shows the probability of randomly selecting subjects whose survival curves are as different as was actually observed, assuming that the null hypothesis is true. We found no statistical association between cancer-specific survival and surgical approach ($P > 0.10$) or between cancer-specific survival and tumor stage, location, or recurrence ($P > 0.10$).

Mean tumor sizes of the patients in groups A and B were 3.5 cm (range, 1.2–4.5) and 3.8 cm (range, 1.6–4.8), respectively. The size of the primary tumor did not seem to influence cause-specific survival ($P > 0.10$). Cancer-specific survival was significantly associated with multifocality (Fisher's exact test, $P = 0.0176$) and presence of metastasis (Fisher's exact test, $P < 10^{-3}$). The appearance of metastatic disease was statistically correlated with tumor stage (χ^2 test, $P = 0.0167$) and multifocality (Fisher's exact test, $P = 0.0017$).

Among the patients who underwent partial nephrectomy, eight (19.5%) had bilateral synchronous lesions.

TABLE I. Morbidity, Renal Function, and Proteinuria in Renal Surgery Patients

	Mean value	
	Group A, partial nephrectomy	Group B, radical nephrectomy
Clearance (ml/min)		
Preoperatively	105	107
2 years postoperatively	95	90
4 years postoperatively	90	80
Proteinuria (mg/24 h)		
Preoperatively	—	—
2 years postoperatively	—	64 (n = 6)
4 years postoperatively	—	98 (n = 6)
Hospitalization (days)	7.3	8.1
Blood transfusion (units)	0.8	1.1
Complications		
Minor flank protrusion	2	1
Wound infection	1	2
Thrombophlebitis	1	—

TABLE II. Patients and Tumor Characteristics

	Group A, partial nephrectomy	Group B, radical nephrectomy
No. of patients	41	48
Mean age, years (range)	64 (44–71)	66 (42–75)
Tumor size, cm (mean)	3.5 (1.2–4.5)	3.8 (1.6–4.8)
Tumor stage, no. (%)		
T1NOMO	10 (24.4%)	9 (18.7%)
T2NOMO	28 (68.3%)	35 (72.9%)
T3aNOMO	3 (7.3%)	4 (8.3%)
Location of neoplasm, no. (%)		
Superior	16 (39%)	19 (39.6%)
Middle	13 (31.7%)	17 (35.4%)
Inferior	12 (29.3%)	12 (25%)
5-year cancer-specific survival	97.5%	98.4%

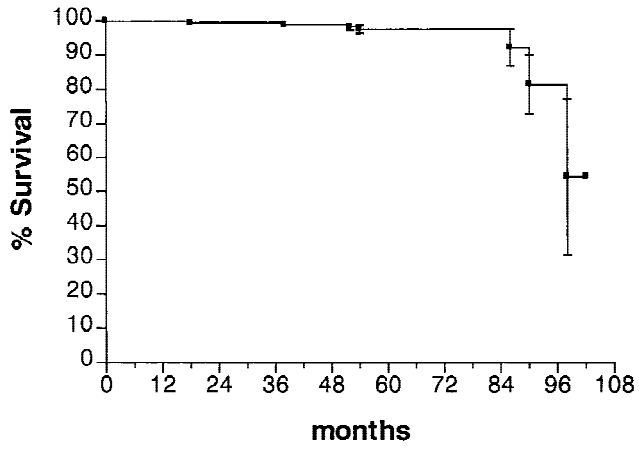

Fig. 1. Cancer-specific survival curve (and standard error of the mean) of patients treated with nephron-sparing surgery (group A).

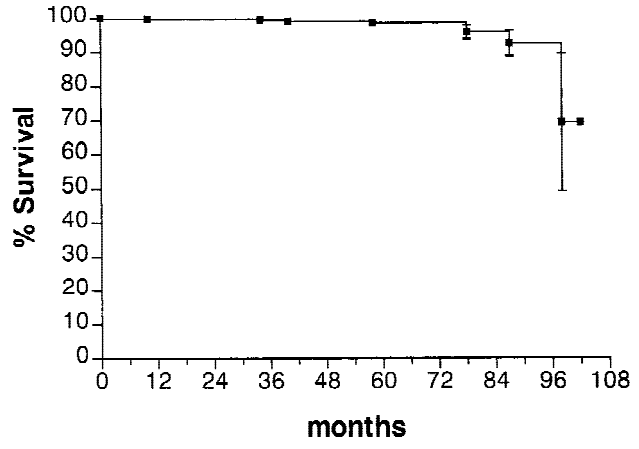

Fig. 2. Cancer-specific survival curve (and standard error of the mean) of patients treated with radical surgery (group B).

Four of these cases had a supplementary nephron-sparing procedure of the contralateral kidney within 12 months after the first operation. Radical nephrectomy of the contralateral kidney was performed in the remaining four cases 6 months after the first operation. Ten patients (24.4%) presented with a solitary kidney due to previous nephrectomy of the contralateral kidney. There were no patients in the radical nephrectomy group with bilateral synchronous lesions or solitary kidney.

Local recurrence was observed in three patients (7.3%) who underwent partial nephrectomy. We did not observe any local recurrence involving the remaining renal fossa in the radically treated group. In our series, the overall incidence of multifocality was 10.4%, as proved by serial sectioning of the removed kidney. It is obvious that pathological confirmation was possible only in group B.

In the nephron-sparing group, the IRU confirmed, but did not improve, the accuracy of the preoperative CT scan evaluation for the assessment of tumor multifocality. IRU revealed better morphological definition of the tumor and its relation with the adjacent collecting system, providing a better depiction of the deep landmarks of our resection. In the last six patients of this series, further ultrasonic search was performed through the newly created fossa after removal of the renal mass, and it was negative in all cases.

DISCUSSION

The increased use of noninvasive abdominal imaging techniques has led to a higher incidental detection of patients with renal cell carcinoma [11]. Radical nephrectomy has been considered the reference standard treatment for localized renal carcinoma with a normally functioning contralateral kidney [1,2]. Many investigators in recent reports present excellent results with nephron-sparing surgery in such cases. Steinbach et al. [15] reported excellent results after nephron-sparing surgery in patients with low-stage, unifocal renal cell carcinomas of 4–5cm without capsule penetration. Velagapudi et al. [16] reported on their experience in cases with small (mean, 3.2 cm), unilateral tumors of stages T1N0M0 and T2N0M0, in which the mean cancer-free period after partial nephrectomy was 4.8 years. Novick et al. [17] reported their findings on 100 patients treated with partial nephrectomy, presenting overall and cancer- specific 5-year survival rates of 67% and 84%, respectively. In a report by Morgan and Zincke [18] on 104 patients, the respective overall and cancer-specific 5-year survival rates were 80% and 88%.

The principal drawback of partial nephrectomy for renal cell carcinoma is the risk of postoperative local tumor recurrence. This risk has been reported to be from 2% to 16% of patients, according to various authors [6,7,12,13,15,18,19]. Licht et al. [20] reported no recurrences after partial nephrectomy in 50 patients with unilateral renal cell carcinoma of 4 cm (stages T1N0M0 and T2N0M0), during a 4-year follow-up period. The etiology of this recurrence is probably due either to incomplete tumor resection or to the presence of undetected prior microscopic satellite lesions in the renal parenchyma. According to Novick et al. [17], patients who present with local recurrence without concomitant presence of distant metastases could be considered candidates for further “sparing” surgical treatment.

The incidence of tumor multifocality has been a source of controversy in the literature. Mukamel et al. [21] reported a 20% incidence of multifocality, Cheng et al. [22] reported an incidence of 7% in kidneys with a primary tumor of 80 mm, and Novick [6] found an incidence of 13%. We believe that multiplicity or multifocality of the tumor is more probable than local recurrence because in our cases recurrence was observed adjacent not to the originally resected area but to more distant parts of the kidney. In 20% of patients with clinically overt carcinomas, there is an increased incidence of unsuspected mul-

tiple tumors [21]. This incidence can be considered responsible for the development of local recurrence or even metastatic disease after segmental resection.

IRU is of paramount importance [11,19,23–25]. Ultrasonic transducers of 7.5 and 10 MHz are recommended for adequate resolution and tissue penetration. Ultrasonography should be completed before the renal artery is clamped and prior to the initiation of hypothermia. The use of IRU was first reported by Gilbert et al. [23]. IRU helps to identify the location and the intraparenchymal extent of the mass, facilitating its accurate resection and ascertaining negative resection margins during nephron-sparing surgery. Campbell et al. [19] suggest that IRU does not aid in the identification of prior unsuspected tumor multifocality. In our study, IRU more clearly showed the mass and its relation to the collecting system, allowing better definition of the deeper landmarks of the resection. Special mention should be made of a technical modification of the ultrasonic approach after removal of the tumor. Following verification of residual tumor absence by the operating microscope, further ultrasonic search was performed through the newly created fossa to look for additional satellite lumps. We believe that this is an important addition to the IRU, which merits further evaluation. It was used only in our last six cases, which were proved negative for multifocality and recurrence during a follow up period of 12–26 months. The small number of cases and the short follow-up do not permit any statistical conclusions to be drawn, but we believe that this modification may prove beneficial in the future, especially with the advent of more advanced ultrasonic probes.

In the literature, there have been a few comparative studies between nephron-sparing and radical surgery. Lerner et al. [13] reported a retrospective study comparing partial nephrectomy with radical nephrectomy in patients matched with respect to age; sex; date of surgery; and tumor location, grade, and pathological stage. They found no significant difference in progression-free intervals or cancer survival between the two operative procedures. Local recurrence appeared in 5% of patients treated with nephron-sparing surgery. Tumor size was of cardinal importance for the outcome of both treated groups.

Butler et al. [26] also reported a comparison of nephron-sparing surgery with radical nephrectomy in patients who present with a single small ($\leq$4 cm) renal cell carcinoma and a normal ipsilateral kidney. The pathologic stage of the masses was T1N0M0 or T2N0M0 in 90% and T3aN0M0 in 10% of the cases. Their results showed that both operative procedures were equally effective in terms of recurrence rate (2% and 3%, respectively) and 5-year survival rate (100% and 97%, respectively).

Brenner et al. [27] brought attention to the hyperfiltration principle, leading to excessive renal blood flow and glomerular filtration rate, which causes continuous activation of the "reserved" glomeruli of the outer cortex. This intrarenal hypertension was considered to be a cause of the progressive glomerular sclerosis that was evident, among other conditions, in cases of surgical loss of renal mass.

Zucchelli et al. [28] essentially confirmed this theory by their observation in uninephrectomized patients who developed significant proteinuria associated with histologic changes of focal segmental glomerulosclerosis several years later. Certainly, there is no unanimous agreement in the literature regarding this principle, but one has to be very cautious to preserve renal function, especially when it is proven that removal of the kidney does not alter patient survival, as was clearly shown in this and other presentations [28–30].

Our study is a retrospective analysis comparing partial and radical nephrectomy in the treatment of renal cell carcinoma. We are aware that few if any prospective comparative studies have been published so far, which we consider reasonable due to the very nature of the problem under investigation. Retrospective studies, such as that presented here with strictly predefined criteria for location of the tumor within the kidney, tumor size, multifocality, recurrence rate, and reasonably long follow-up, are valuable for initial determination of efficacy.

In view of our data, we propose segmental renal resection for unifocal small adenocarcinoma of the kidney in preference to radical surgery. We have used and recommend renal hypothermia and contact IRU to better define the surgical landmarks of the renal mass, especially the mass in relation to the collecting system and possible remaining satellite lesions. Operative magnification via the operating microscope further helps in the verification of tumor-free renal edges, but its use has to be further evaluated in more cases.

Having been taught and having practiced the time-honored method of radical nephrectomy for cancer of the kidney, we believe it is important to prove that a similar, if not better (for the conservative group), survival is achieved in these two groups of patients. Certainly, for almost any treatment method, a prospective randomized trial with a very large series of patients is optimal. However, when designing a prospective study, one is faced with the need to justify the sacrifice of renal units, which in view of data presented in the literature, the undersupply of donors for transplantation, and the projected increased population survival, demands at least further elaboration.

In conclusion, we consider that our study enhances the trend toward the conservation of kidneys, taking into account the above-stated strict inclusion criteria. Further follow-up and certainly an extended database of patients submitted to radical or conservative surgery are needed to provide final unequivocal conclusions.

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